Please cancel claim 3.

REMARKS

Status of the Claims

Claims 1-4 and 6-13 are pending. Claims 6-10 are allowed. Claims 1, 2 and 11-13 are rejected. Claims 3-4 are objected to. Claim 1 is amended. Claim 3 is cancelled.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned "**VERSION WITH MARKINGS TO SHOW CHANGES MADE**". No new matter has been added. Reconsideration of the pending claims is respectfully requested.

Amendments to the claims

Claim 1 has been amended. Claim 3 has been cancelled. No new matter has been added.

The 35 U.S.C. §102(b) rejection

Claims 1-2 are rejected under 35 U.S.C. §102(b) as being anticipated by **Corral-Debrinski** *et al.* (*Mutation Research* 275: 169-180 (1992)). Applicant respectfully traverses this rejection.

The Examiner states that because the claims are drawn to collecting any tissue, **Corral-Debrinski** anticipates the claimed invention; "any tissue" encompasses not only arteries and blood, but also cardiac tissue as taught by **Corral-Debrinski.**

Corral-Debrinski teaches quantitative PCR to compare the levels of a common 4977 base-pair deletion in mitochondrial DNA between post-mortem heart samples from normal individuals and individuals with coronary atherosclerotic disease. **Corral-Debrinski** fails to anticipate the instant invention, however, in that **Corral-Debrinski** does not teach a method of evaluating the atherosclerotic state of an individual. **Corral-Debrinski** analyzed cardiac tissues from pathology samples, but provides no teaching that one could analyze mitochondrial damage in the actual tissues involved in atherosclerosis, specifically the arteries and the blood. Further, **Corral-Debrinski** examined damaged hearts from deceased patients. Claim 1 has been amended to incorporate the

elements of claim 3, adding the limitation that the individual recited has at least one risk factor associated with atherosclerosis. The aortic samples obtained from deceased patients taught by **Corral-Debrinski** could not be obtained from an individual having a risk factor for atherosclerosis.

The PCR amplification taught in **Corral-Debrinski** was limited to the detection of mutations in the mitochondrial DNA of the heart tissue. In contrast, Applicants' invention describes the measurement of oxidative damage in the mitochondrial DNA template in the form of reversible oxidative lesions, as well as mutations. The detection of oxidative DNA lesions is not taught by **Corral-Debrinski.**

In conclusion, **Corral-Debrinski** does not teach each and every element of claim 1, as amended. Therefore, Applicants respectfully request that the rejection of claims 1-2 under 35 U.S.C. §102(b) as anticipated by **Corral-Debrinski** be withdrawn.

The 35 U.S.C. §103(a) rejection

Claims 11-13 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Yan** *et al.* (*Circulation* 96 (8): Suppl. P. I605 (1997) or **Corral-Debrinski** *et al.* (*Mutation Research* 275: 169-180 (1992) in view of **Herrnstadt** *et al.* (U.S. Pat. No. 6,218,117, April 2001). Applicant respectfully traverses the Examiner's rejection.

The Examiner states that **Yan** teaches an *in vivo* relationship between reactive oxygen species and mitochondrial DNA damage in atherosclerosis; specifically that quantitative PCR assays of diseased and normal human aortic tissues show greater mitochondrial DNA damage in diseased tissues. **Corral-Debrinski** teaches an association of mitochondrial DNA damage with coronary atherosclerotic heart disease, by sampling cardiac tissue and estimating mitochondrial DNA damage in the form of DNA deletions, using PCR. Neither **Yan** nor **Corral-Debrinski** teaches a method of determining the efficacy of a drug by administering a drug to a sample and determining the level of mitochondrial DNA damage. However, **Herrnstadt** teaches methods for identifying agents for treating a disease associated with altered mitochondrial function, by

comparing the ratio of the amount of DNA from a sample obtained before contacting a biological source with a candidate agent with the ratio from a sample obtained after such contact. According to the Examiner, therefore, one skilled in the art would be motivated to combine the teachings of **Herrnstadt** with those of the cited references to evaluate possible treatments for the risks of atherosclerosis.

Applicant respectfully argues that the teachings and suggestions of the cited references do not contain all the claim elements of the present invention, which is necessary to establish a prima facie case of obviousness under 35 U.S.C. §103(a) (M.P.E.P. §2142). The teachings of **Corral-Debrinski** and **Yan** do not include the measurement of mitochondrial DNA in a sample from an individual who may be at risk for atherosclerosis, wherein a decrease in mitochondrial DNA damage subsequent to administering a drug is indicative of a treatment that reduces the risk of atherosclerosis. **Herrnstadt** only teaches the quantification of the amounts of extramitochondrial DNA and mitochondrial DNA in a sample, as a ration r, to determine the efficacy of a drug to treat a disease associated with altered mitochondrial function.

Herrnstadt does not teach the quantification of mitochondrial DNA damage as the criterion for evaluating the efficacy of a drug to reduce the risk of atherosclerosis, nor does **Herrnstadt** mention atherosclerosis as a disease associated with altered mitochondrial function. Considering the reference as a whole, **Herrnstadt** teaches the criterion of alterations in mitochondrial function, as measured by the amounts of DNA present in the sample, as a way to evaluate the efficacy of a drug to treat a disease associated with such alterations in function. **Herrnstadt** does not teach or suggest that the quantification of mitochondrial DNA damage be a possible criterion to evaluate a reduction in the risk of atherosclerosis by treatment with a drug.

A prima facie case of obviousness also requires that the teaching or suggestion to combine the elements of the claimed invention with a reasonable expectation of success must be found in the prior art, and not based on Applicant's disclosure (M.P.E.P. §2142). Applicant respectfully submits that the cited references do not contain all of the limitations of claims 11-13, and that therefore the requisite motivation to combine the claimed elements with a reasonable expectation of success is not present. In order to be

motivated to combine the elements of the claimed invention, one skilled in the art would require the teachings of the present application, so that a rejection for obviousness based on the references cited constitutes an impermissible hind-sight rejection (M.P.E.P. §2142). In addition, the fact that references can be combined or modified does not render the combination obvious unless the prior art also suggests the desirability of the combination (M.P.E.P. §2143.01). Applicant respectfully submits that because **Herrnstadt** teaches a completely different criterion for evaluating the efficacy of a drug, such a desirability of combining the claimed elements is not present.

Accordingly, Applicant respectfully requests that the rejection of claims 11-13 under 35 U.S.C. §103(a) be withdrawn.

Claim Objections

The Examiner's objection to claims 3-4 as dependent on a rejected claim is respectfully traversed. The elements of claim 3 have been incorporated into amended claim 1, upon which claim 4 depends. The objection to claim 3 is moot, because claim 3 has

been cancelled. Accordingly, Applicant respectfully requests that the objection to claims 3-4 be withdrawn.

This is intended to be a complete response to the Office Action mailed March 11, 2003. If any issues remain outstanding, the Examiner is respectfully requested to telephone the undersigned attorney of record for immediate resolution.

Respectfully submitted,

DATE: April 28, 2003

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Please amend claim 1 as follows:

1. (Twice amended) A method of evaluating the atherosclerotic state of an individual having at least one risk factor associated with atherosclerosis, comprising the steps of:

(d) collecting a tissue of interest from said individual;

(e) determining the amount of mitochondrial DNA damage in said tissue of interest; and

(f) comparing the amount of mitochondrial DNA damage in the tissue of interest from said individual to the amount of mitochondrial DNA damage in a tissue of interest from a control individual who does not have atherosclerosis, wherein a greater amount of mitochondrial DNA damage in said individual at risk than in said control individual is indicative of atherosclerosis in said individual, wherein said mitochondrial DNA damage is assessed by a measurement selected from the group consisting of measurement of mitochondrial mRNA production, measurement of mitochondrial protein production, measurement of changes in mitochondrial

oxidative phosphorylation and measurement of changes in mitochondrial ATP production.

Please cancel claim 3.